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TITLE: Preventing Epilepsy after Traumatic Brain Injury

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The purpose of this study is to determine the safety and tolerability of topiramate (TPM) in the treatment of early seizures following traumatic brain injury (TBI), and to compare the efficacy of TPM to prevent early seizures to the standard of care (phenytoin). A secondary objective is to obtain the data necessary to design a randomized clinical trial to determine if TPM can prevent epilepsy and improve neurological outcome after TBI. In the first two years of the study, we formulated the protocol and all documents required by regulatory bodies. These were approved by the IRB at the University of Pennsylvania, HRPO at the USArmy, and the FDA. The infrastructure for the study was established, relevant personnel were hired and the patient recruitment methods, interactions with the trauma center, neurosurgical services, EEG laboratory, pharmacy, etc. were organized. Subject recruitment began. Initial subject recruitment was very slow and the protocol was revised to eliminate several major obstacles. We have enrolled 5 subjects into the study; two in the phenytoin arm, one in the short term topiramate , one in the 3 month topiramate arm; one subject was withdrawn after testing positive for illicit drug use. We have also organized a NINDS-sponsored workshop on Biomarkers for Epileptogenesis and a program to assist TBI veterans.

**15. SUBJECT TERMS**

None listed.

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**INTRODUCTION:**

The purpose of this study is to determine the safety and tolerability of topiramate (TPM - Topamax®) in the treatment of early seizures following traumatic brain injury (TBI), and to determine if topiramate can prevent early seizures better than the current standard of care (phenytoin). A secondary objective is to obtain the data necessary to design a randomized clinical trial to determine if topiramate can prevent epilepsy and improve neurological outcome after TBI. In addition, the study proposed to help identify biomarkers for the process of epileptogenesis that could be used to predict which patients with TBI were most likely to develop posttraumatic epilepsy, and as an assay for effects of potential therapies. Approximately 90 subjects at the University of Pennsylvania were initially earmarked for participation in this study. Patients with moderate to severe head trauma who meet entry criteria will be randomized to one of three arms of the study. All subjects will receive a loading dose of phenytoin within several hours of being admitted to the trauma/neurosurgical unit, as part of the standard of care for such individuals. The subjects will then be randomized to three experimental arms. One arm will receive topiramate for up to six additional days, the second arm will receive topiramate for three months, and the third, control arm will continue to receive phenytoin for six more days (current standard of care). EEGs will be performed as soon as possible and, as much as possible, continuously for up to seven days from onset of the study. The subjects will be monitored for clinical seizures, subclinical, electrographic seizures, and recovery of function. Additional EEG analysis will examine potential biomarkers for epileptogenesis. Blood samples, and where possible without additional invasive procedures, CSF samples, will be collected and stored for analysis of possible biochemical biomarkers of epileptogenesis. Subjects will also have MRI scans at one month and twelve months to assess structural damage to the brain. Subjects will be followed for two years to determine if epilepsy subsequently develops and to assess level of functional recovery.

**BODY:**

The original Statement of Work indicated four sets of projects to be accomplished in the first three years of the grant. We have completed most of these objectives, except for the data analysis portion (see below).

In the first year of the study, we formulated the protocol for the clinical trial, created case report forms and case books, and developed the informed consent documents and other documents required by regulatory bodies. All of these were submitted to the IRB at the University of Pennsylvania, the US Army, HRPO, and the FDA. The approval process for this protocol, especially from the HRPO, took approximately one year. During this time we established the infrastructure for the study, hired relevant personnel and organized the patient recruitment methods, interactions with the trauma center, neurosurgical services, EEG laboratory, pharmacy, etc. in order to conduct the research. Patient recruitment is now commencing.

Once all the regulatory and infrastructural issues were accomplished, we began attempting to recruit subjects for the study.

Below we present the original SOWs (in italics) and our accomplishments over the first two years:

**SOW - Task 1:** *Develop instruments for a pilot (and subsequently, full) clinical trial for epilepsy prevention after head injury.* This has been accomplished by the development of the clinical trial protocol, informed consent, case books, and regulatory documents. All of these have received approvals by the University of Pennsylvania IRB, the USArmy HRPO, and the FDA. This approval process took approximately one year to complete. The most prolonged component was the HRPO.

a. *Develop the web-based clinical trial instrument now being tested at the University of Pennsylvania for use in clinical trial for epilepsy prevention after head injury. (This study management tool will act as the primary system for managing all aspects of the clinical trial, including functioning as a central repository of all research studies and associated personnel, budget set-up and financial tracking, self-population of standard forms, tracking of IRB and other regulatory approvals, subject scheduling and processing, and overall study tracking. It is expected that once this instrument is fully implemented for this neuroprotection study, it will be easily reformulated for other neuroprotection trials.)* We have accomplished this task but have not yet incorporated the web based clinical trial instrument. Instead, we developed these tools internally. We expect to attempt to employ a web based mechanism as the trial progresses. We investigated several software packages designed specifically for use in clinical trials of various sizes, that would be suitably powerful, but also suitably "user friendly" to permit study personnel to enter data efficiently and also permit continuous data monitoring and evaluation. We purchased licenses for the Science Trax Software package (Study Trax). This software is especially designed for use in research. Users can easily learn and adopt the application. The analytical process is streamlined because the user has the ability to create analysis-ready data sets that export to statistical packages. This eliminates the dependency on technical staff to create and export data and it also reduces the burden on the staff by allowing the subjects to enter data via the internet. Currently our patients are being entered into this software.
b. *Develop web-based clinical data base for use in epilepsy prevention trial.* Similarly, we chose to use a simpler, more easily available data base for the early pilot program, as the expense for developing a more comprehensive web-based data base was beyond our budgetary capacity.
c. *Develop brain image data base (BRAID) that can be combined with the clinical data base for use in epilepsy prevention trial.* We have established appropriate MRI protocols for the TBI study in collaboration with the neuroradiology group at the University of Pennsylvania to permit collection of MRI data on the TBI patients in the study and incorporate these images into a BRAID data base being developed at the University. Subjects admitted to the study thus far have had "early" MRIs at 1 month after the TBI. Subjects are scheduled for follow up MRIs at 12 months post TBI.
d. *Combine instruments developed in above into a specific clinical protocol for a 3 arm study designed to prevent epilepsy after moderate to severe head injury.* This has been accomplished and has passed all regulatory requirements.

**SOW - Task 2:** *Develop the infrastructure for implementation of randomized double blind trial to prevent epilepsy after head injury.* This has been accomplished.

a. *Establish procedures with trauma team and ER personnel for identifying candidates for epilepsy prevention trial.* We initially mobilized collaborators in the ER, the Trauma Unit, and our newly established Neurological/Neurosurgical Intensive Care Unit to participate in the study. We held meetings with the teams to provide in-service training and will continue to do so as the protocol launches. As we began implementing the study, it became apparent, for a variety of technical reasons, that we would be unable to recruit patients into the study within the original 12 hour window that we specified, and that we would not be able to start the topiramate before many of the patients received a phenytoin load (standard of care that did not require informed consent by the patient or a legally authorized surrogate.) We then changed the protocol to increase the entry window to 24 hours and to have every subject receive a loading dose of phenytoin before being randomized to up to 6days of topiramate or 3 months of topiramate. This allowed us to begin successfully recruiting subjects. Despite these changes, however, recruitment continued at a slow pace. Reanalysis of the patients entering HUP with traumatic brain injury indicated that a significant number arrived outside the 24 hour window, often after stabilization at outside hospitals. We have therefore modified the protocol

to open the window of eligibility to 72 hours and have obtained regulatory approval from the Penn IRB, FDA, and are awaiting approval from HRPO.

b. *Establish procedures to obtain appropriate consent from subjects that are too impaired to provide conventional informed consent. This would involve obtaining consent from individuals who are legally identified as being able to provide consent or by obtaining community consent.* This has been accomplished to the satisfaction of all regulatory bodies involved. This is not a trivial issue, since most of the subjects will arrive to the ER in a state that will prevent them from being able to provide informed consent (e.g. either comatose or mentally impaired). As mentioned above, our initial protocol required administration of the first dose of antiseizure drug by 12 hours from the TBI, so we needed to reach the appropriate, legally sanctioned individual associated with each subject to provide informed consent. This could not be done with either waiver of consent, or "community consent" under current HRPO guidelines, and we were not permitted to obtain informed consent over the telephone, even temporarily. Thus, we had to rely on being able to communicate directly with appropriate surrogates within 12 hours of the TBI. This required that our study personnel, mainly physicians and EEG technologist, be available 7 days per week, 24 hours per day. As mentioned above, it turned out to be virtually impossible to identify perspective candidates for the study and identify appropriate individuals for obtaining informed consent in person, within the guidelines initially established, as especially as individuals with TBI often presented late at night, on weekends, and with appropriate "consenters' unavailable. As discussed above, for this and other reasons, the protocol has been revised twice.

c. *Develop and promulgate standardized treatment protocol for head injured patients.* This was accomplished in collaboration with our neurosurgical team.

d. *Establish pharmacy program for administration of study medications in a double blind manner.* This was accomplished with the HUP Interventional Drug Services (IDS).

e. *Establish procedures for obtaining continuous EEG monitoring for up to 7 days post head injury.* This was accomplished by recruiting a talented EEG technologist to perform and monitor these tests and be dedicated to this protocol. She already has experience performing continuous EEGs on TBI patients from a preliminary study (without drug intervention) that we have begun at the University of Pennsylvania. In addition, we are using EEG electrodes that are CT and MRI compatible so they will not need to be removed each time a patient with TBI requires an emergency study as part of their clinical care. These electrodes are part of the standard care for patients in the Neurological Intensive Care Unit who are on continuous EEG monitoring.

f. *Establish internal and external data and patient safety monitoring boards.* We have engaged an outside clinical trials auditing group to periodically audit our clinical trial and make sure that there are no serious deviations from our protocol. We have established an internal safety review process and are in the process of establishing an external DSMB, now that we have 5 patients enrolled in the study. This is not required by the regulatory bodies, but we thought it would be a useful addition to the study.

**SOW - Task 3:** *Implement pilot clinical trial to prevent the development of epilepsy in individuals with moderate to severe head injury by 7 day and 3 month treatment with topiramate*

a. After receiving approval from all the relevant regulatory agencies, we began to screen TBI patients arriving in the trauma unit of the Hospital of the University of Pennsylvania for entry into the study. At this point we encountered two major and unexpected problems. First, because of our inability to enter subjects into the study based on either a waiver of informed consent or community consent, we needed to have a personal interaction with the legally designated representative of the patient with TBI in order to obtain informed consent to enter

them into the study. Because moderate to severe TBI often results in impaired consciousness, judgment and cognitive function, we most often were unable to obtain informed consent from the subjects, themselves. This proved to be exceedingly difficult within the original 12 hour window for admission that was initially established. Secondly, although before the study had begun, we analyzed initial treatment of TBI patients at HUP and determined that many, for a variety of legitimate reasons, did not receive phenytoin within the first 12 hours, once the study commenced and administration of an antiepileptic drug became part of the protocol for all patients with moderate to severe TBI, it was impossible to withhold phenytoin for the12 hours during which informed consent, randomization, medication distribution, etc was occurring in the protocol. Third, a significant number of patients arrived at HUP close to, or just after, the 12 hour window, so they could not be recruited for the clinical trial.

b. After screening more than 100 patients over the first 6 months after the protocol was approved, we determined that the pilot program would need to be modified in order to accomplish its goals. Accordingly, we submitted a revised protocol to the IRB at the University of Pennsylvania, the FDA and the USArmy HRPO. The revised protocol now allows all subjects to receive a loading dose of phenytoin within 3 hours of being admitted to the trauma unit (standard of care), allows for a 24 hour window for admission to the study, and lowers the initial, loading, dose of topiramate. The remaining elements of the pilot trial remain as they were. We are confident that these changes will permit recruitment to proceed.
c. Although the revised protocol did permit successful recruitment of subjects into the study, this continued to be an unacceptably slow process. This was surprising as our preliminary studies indicated that we would be able to accrue many more subjects then we subsequently did. One possible explanation, as discussed in local newspapers, is that the “fire power” of guns in the streets of Philadelphia has increased over the last few years, so it is possible that individuals who had gunshot wounds to the head were now much more seriously injured (often fatally) and this cohort of potential subjects was much less available then in prior years. Furthermore, we lost a significant number of possible candidates because they had a history of drug addiction or had illicit drugs found during routine admission toxicology screens or were involved in a police matter. In addition, when we analyzed our recruitment data, we realized that significant numbers of patients were reaching Penn outside the 24 hour window, often because they were first seen at outlying hospitals and were then transferred to The Hospital of the University of Pennsylvania (HUP). Consequently, we have revised our protocol to allow a 72 hour window after TBI. This was submitted to the Penn IRB, FDA, and HRPO, and has been approved by two of the regulatory bodies and we are awaiting approval from the HRPO.

**KEY RESEARCH ACCOMPLISHMENTS:**

- Write clinical protocol
- Develop informed consents
- Develop case report forms
- Explore various software packages designed for developing clinical trial data bases
- Submit documents to University of Pennsylvania IRB and obtain approval
- Submit documents to US Army HRPO and obtain approval
- Submit documents to FDA and obtain IND
- Recruit EEG technologist
- Arrange for randomized drug distribution with Pharmacy
- Arrange collaborative efforts with emergency room, neurosurgery and trauma units
- Establish mechanism for rapid identification of subjects upon arrival in trauma unit
- Develop in service training for relevant personnel

- Establish brain imaging protocols
- Revise protocol, informed consent and case report forms based on initial unsuccessful recruitment period.
- Recruit 5 patients into the study. Follow them through their initial hospitalizations, in rehab (when appropriate), and as outpatients.
- Obtain follow up EEGs and MRIs on subjects enrolled in the study.
- Organize and lead an NINDS sponsored workshop on Biomarkers for Epileptogenesis
- Identify electrophysiological, imaging, biochemical and genomic biomarkers that might be useful in monitoring the process of epileptogenesis and the response to potential therapies

**REPORTABLE OUTCOMES:**

To date, there are no reportable outcomes with regard to the specifics of the pilot clinical trial, as the protocol is in its recruitment phase. The results of the Biomarkers for Epileptogenesis workshop were presented in March, 2007 at the 9th bi-annual Antiepileptic Drug Trials meeting held in Florida. Several of the conclusions from this workshop were incorporated as NINDS guidelines in the Curing Epilepsy Conference that was held in Bethesda, MD in March 2007. Dr. Dichter delivered an invited lecture at the Merritt-Putnam Symposium during the Annual Meeting of the American Epilepsy Society that focused on translation of basic science discoveries into therapies to prevent epilepsy. This lecture highlighted issues related to clinical trials in anti-epileptogenesis and emphasized how little clinical research is being performed in this area throughout the US and the world.

**CONCLUSION:**

In the first year of this grant we successfully completed all the pretrial components and received all the necessary regulatory approvals. This included performing up to7 days of continuous EEGs on TBI patients who were not part of this research protocol and who did not receive any specific anti-epileptogenic seizure intervention beyond current standard of care. Developing the infrastructure for this kind of trial and successfully navigating all the potential issues in an acute intervention trial in severely injured patients was not a trivial task. Similarly, coordinating multiple medical teams, each of which is focused on their own tasks with regard to major trauma cases (e.g. trauma surgeons, neurosurgeons, emergency room personnel, nurses, pharmacy, etc.) was also a significant accomplishment. By the middle of the second year we began recruiting subjects. After screening more than 100 TBI patients in our trauma unit over six months, we realized that there were major procedural obstacles to completing the pilot trial as originally formulated (see SOW - Task 3, above) and we modified the protocol to circumvent these problems without compromising the study. During the third year of the grant we actively recruited all eligible patients appearing at HUP and did not "lose" more than a very few patients. However, it became clear that the recruitment continued to be very slow. The protocol was modified to allow a longer entry period and all the relevant approvals have been submitted for this modified protocol; approval has been received from the Penn IRB and the FDA and is pending for the HRPO. Recruitment of new subjects and follow up of subjects in the study are continuing.

In addition to the direct pilot study in preventing epilepsy after TBI, we have a achieved a significant accomplishment with regard to a very important issue related to this study and one which was not submitted as a major part of this grant. We initiated a program in conjunction with the National Institutes of Neurological Diseases and Stroke to hold a conference on Biomarkers of Epileptogenesis. Our reasoning was that we were developing a unique resource for trying to study this issue in humans as an adjunct to our study and with no additional risk to our patients. We are

collaborating with the only two groups in the US who have been, or are currently, engaged in epilepsy prevention trials – The University of Washington (who recently completed their third, unfortunately negative, clinical trial to prevent epilepsy after TBI) and a group in Washington, DC launching a small pilot trial of preventing epilepsy after TBI (although with less severely injured patients than we are studying and without continuous EEG recordings). This conference brought together researchers at both the clinical level and animal model level to consider what is known about the process of epileptogenesis and how we might develop biomarkers of the process using electrophysiology (including highly sophisticated signal processing techniques that are not standard in this field), imaging, biochemical markers in CSF and serum, and genomics. The results of this conference have been presented at an international meeting on new antiepileptic drugs and at lectures at the annual meeting of the American Epilepsy Society.

A related accomplishment, also not directly part of the original grant, but something that was inspired and stimulated by the clinical trial being sponsored by the US Army, was the establishment of Operation Giveback by Dr. Dichter and the American Epilepsy Society. As more and more information was being released about the extent of TBI in the returning veterans of the gulf wars, Dr. Dichter became increasingly concerned about the possibility that many of these injured veterans would be susceptible to developing posttraumatic epilepsy, months or even years after returning to the US. Some of these seizures might not be recognized as seizures, if they remained partial and did not generalize. Thus, these veterans might be assumed to be suffering from continued cognitive or behavioral disorders when, in fact, they may have been experiencing treatable seizures. Dr. Dichter developed a program, called “Operation Giveback” to galvanize the epilepsy community to try to make sure none of these veterans “fell through the cracks” of optimal medical diagnosis and care for their possible post-TBI epilepsy. He proposed this plan to the AES, as well as to other national neurology organizations, and it was adopted by the AES, and enthusiastically endorsed by the other organizations. A task force was formed to determine where the needs were and how AES members could assist the DOD and DVA, as well as working in the private sector, to facilitate care for the possible posttraumatic epilepsy that might develop in the wounded veterans. Educational programs were developed to try to reach the veterans, their families, and primary care providers, to make everyone aware of this problem, especially the subtleties of the seizure presentations (see AES website). In addition, Dr. Dichter is working with the epilepsy specialists within the DVA to enhance and expand services available to veterans with regard to epilepsy diagnosis and treatment.

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**APPENDICES:** N/A

**SUPPORTING DATA**: N/A